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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/816,465	04/01/2004	Sonia Moreno-Lopez	MORENO-LOPEZ	8524

20151 7590 04/02/2009

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
04/02/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/816,465	MORENO-LOPEZ ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/23/09 has been entered. Applicant's amendment and response filed concurrently with the RCE have also been entered. Claims 1-41 are canceled and new claim 44 has been added. Claims 42-44 are currently pending in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in a previous office action.

Priority

Applicant's claim for foreign priority based on applications filed in Germany on October 2, 2001 or November 12, 2001, is acknowledged. Certified copies of both documents, DE 101 56 678.6 and DE 101 48 697.9, both in German, have now been received in the instant application as required by 35 U.S.C. 119(b).

Claim Rejections - 35 USC § 102

The rejection of claim 43 under 35 U.S.C. 102(a) as being anticipated by Schirmbeck et al. (June 2001) J. Mol. Med., Vol. 79, 343-350, is withdrawn in view of the Declaration under 37

CFR 1.131 by inventors Sonia Moreno-Lopez and Marcos Timon-Jimenez which establishes that the inventors were in possession of the invention as claimed in claim 43 prior to the publication date of Schirmbeck et al. As such, Schirmbeck et al. is disqualified as prior art.

Claim Rejections - 35 USC § 103

The rejection of claim 42 under 35 U.S.C. 103(a) as being unpatentable over Schirmbeck et al. (June 2001) J. Mol. Med., Vol. 79, 343-350, in view of Makkerh et al. (1996) Current Biology, Vol. 6(8), 1025-1027, is withdrawn in view of the Declaration under 37 CFR 1.131 by inventors Sonia Moreno-Lopez and Marcos Timon-Jimenez which establishes that the inventors were in possession of the invention prior to the publication date of Schirmbeck et al. As such, Schirmbeck et al. is disqualified as prior art, and Makkerh et al. by itself does not render the claimed invention obvious.

The following new grounds of rejection under 35 U.S.C. 103(a) have been found to apply to the claims as amended.

Claims 42 and 44 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over McCluskie et al. (1999) Mol. Med., Vol. 5, 287-300 (IDS of 7/04, ref AU), in view of U.S. Patent No. 6,451,593 (2002), effective filing date of at least May 12, 1999, hereafter referred to as Wittig et al. (previously cited on 892 of 9/22/06), and Makkerh et al. (1996) Current Biology, Vol. 6 (8), 1025-1027.

The applicant claims methods of eliciting an immune response in a living being comprising providing a product comprising a TH1-cellular mediated immune response eliciting vaccine comprising a DNA expression construct comprising a covalently closed linear DNA molecule comprising a linear double stranded region comprising a coding sequence under control of a promoter, where the single strands forming the double strand are linked a short single stranded loops of DNA, and where the construct is covalently linked to an oligopeptide, wherein the construct encodes a hepatitis antigen, and wherein the oligopeptide consists of PKKKRKV (SEQ ID NO:4), and administering the vaccine using intradermal injection into a living being.

McCluskie et al. teaches a genetic vaccine for eliciting Th1 type cellular immune response against hepatitis comprising a plasmid vector encoding a hepatitis antigen and methods of administering the vaccine using intradermal injection to generate hepatitis antigen specific CTL and antibodies (McCluskie et al., pages 289 and 291-294). In particular, McCluskie et al. demonstrates that intradermal injection of plasmid encoding the major surface protein of Hepatitis B envelope protein generates significant CTL responses and predominantly Th1 type antibody responses at 4 weeks post-vaccination (McCluskie et al., pages 291-292, Figures 1 and 2).

McCluskie et al. differs from the instant invention in that the DNA expression construct is a plasmid and in that the DNA is not covalently linked to an oligopeptide such as PKKKRKV. Wittig et al. supplements McCluskie et al. by teaching dumbbell shaped DNA expression constructs comprising covalently closed linear DNA that contains only a coding sequence operably linked to a promoter and polyA termination sequence where the linear ends are linked by short single stranded loops of DNA, and wherein the construct is further covalently linked to

a peptide which directs transport of the construct across a cell's endosome or into the nucleus (Wittig et al., claims 1-11, and columns 5-8)). In particular, Wittig et al. specifically teaches the use of the nuclear localization sequence (NLS) from SV40, a sequence which inherently comprises PKKKRKV (Wittig et al., column 5). Wittig et al. also teaches a vaccine comprising this construct for treating infectious diseases (Wittig et al., columns 1 and 8). Wittig et al. further provides motivation for using a dumbbell DNA expression construct linked to a peptide over a plasmid DNA expression construct. Wittig et al. teaches that because the dumbbell construct consists only of a promoter-gene-terminator sequence, these constructs have none of the disadvantages of plasmid constructs, which include their size, which inhibits fast transport into the cell's nucleus, and the presence of unwanted background sequences, including bacterial sequences, which can lead to unintended immune responses (Wittig et al., columns 2-3, bridging paragraph).

While Wittig et al. does teach to use an oligopeptide covalently attached to the DNA construct for nuclear transport, and teaches the use of the NLS from SV40, Wittig et al. does not specifically teach that the peptide consists of PKKKRKV. However, at the time of filing, the exact nuclear localization sequence (NLS) of SV40 was known. Makkerh et al. teaches that the sequence consisting of PKKKRKV is the defined nuclear localization sequence of SV40, which can be used to target heterologous molecules to the nucleus (Makkerh et al., page 1025, and Table I, page 1027).

Therefore, based on the advantages to using dumbbell DNA expression constructs over plasmid constructs for immunization as taught by McCluskie et al., the motivation to covalently attach a peptide such as an NLS from SV40 also provided by Wittig et al., and the known

sequence of the NLS peptide from SV40 as provided by Makkerh et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to use a dumbbell DNA construct encoding hepatitis antigen linked to the defined NLS peptide PKKKRKV of Makkerh et al. according to the teachings of Wittig instead of a plasmid construct in the methods of immunizing against hepatitis taught by McCluskie et al. Further, based on the substantial guidance for making dumbbell constructs provided by Wittig et al., and the teachings of Wittig et al. that such constructs can be used as vaccines for infectious diseases, the skilled artisan would have had a reasonable expectation of success in making a dumbbell DNA expression construct encoding a hepatitis antigen covalently linked to a peptide such as the PKKKRKV peptide from SV40, and in administering the construct by intradermal injection as taught by McCluskie et al. to elicit immune responses in a living being.

Claim 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over McCluskie et al. (1999) Mol. Med., Vol. 5, 287-300, (IDS of 7/04, ref AU), in view of U.S. Patent No. 6,451,593 (2002), effective filing date of at least May 12, 1999, hereafter referred to as Wittig et al. (of record), and Liu et al. (2001) Biomacromolecules, Vol. 2, 362-368 (of record). Please note that although the declaratory evidence demonstrates possession of a MIDGE vector linked to an NLS prior to 2001, the declaratory evidence provided does not disclose an NLS with the sequence YGRKKRRQRRR. As such, possession of such a MIDGE with the NLS sequence YGRKKRRQRRR has not been demonstrated prior to the effective filing date of 10/2/2001. Therefore, Liu et al. qualifies as prior art.

The applicant claims methods of eliciting an immune response in a living being comprising providing a product comprising a TH1-cellular mediated immune response eliciting vaccine comprising a DNA expression construct comprising a covalently closed linear DNA molecule comprising a linear double stranded region comprising a coding sequence under control of a promoter, where the single strands forming the double strand are linked a short single stranded loops of DNA, and where the construct is covalently linked to an oligopeptide, wherein the construct encodes a hepatitis antigen, and wherein the oligopeptide consists of YGRKKRRQRRR (SEQ ID NO:3), and administering the vaccine using intradermal injection into a living being.

McCluskie et al. teaches a genetic vaccine for eliciting Th1 type cellular immune response against hepatitis comprising a plasmid vector encoding a hepatitis antigen and methods of administering the vaccine using intradermal injection to generate hepatitis antigen specific CTL and antibodies (McCluskie et al., pages 289 and 291-294). In particular, McCluskie et al. demonstrates that intradermal injection of plasmid encoding the major surface protein of Hepatitis B envelope protein generates significant CTL responses and predominantly Th1 type antibody responses at 4 weeks post-vaccination (McCluskie et al., pages 291-292, Figures 1 and 2).

McCluskie et al. differs from the instant invention in that the DNA expression construct is plasmid and in that the DNA is not covalently linked to an oligopeptide such as YGRKKRRQRRR. Wittig et al. supplements McCluskie et al. by teaching dumbbell shaped DNA expression constructs comprising covalently closed linear DNA that contains only a coding sequence operably linked to a promoter and polyA termination sequence where the linear ends

are linked by short single stranded loops of DNA, and wherein the construct is further covalently linked to a peptide which directs transport of the construct across a cell's endosome or into the nucleus (Wittig et al., claims 1-11, and columns 5-8)). Wittig et al. also teaches a vaccine comprising this construct for treating infectious diseases (Wittig et al., columns 1 and 8). Wittig et al. further provides motivation for using a dumbbell DNA expression construct linked to a peptide over a plasmid DNA expression construct. Wittig et al. teaches that because the dumbbell construct consists only of a promoter-gene-terminator sequence, these constructs have none of the disadvantages of plasmid constructs, which include their size, which inhibits fast transport into the cell's nucleus, and the presence of unwanted background sequences, including bacterial sequences, which can lead to unintended immune responses (Wittig et al., columns 2-3, bridging paragraph).

While Wittig et al. does teach to use an oligopeptide covalently attached to the DNA construct for nuclear transport, including viral sequences, Wittig et al. does not specifically teach that the peptide consists of YGRKKRRQRRR. Liu et al. supplements both Wittig et al. and Schirmbeck et al. by teaching that the oligomeric peptide sequence YGRKKRRQRRR from the protein transduction domain of HIV TAT protein mediates the transduction of molecules covalently attached to the peptide into cells (Liu et al., page 363, column 1). Therefore, based on the advantages to using dumbbell DNA expression constructs over plasmid constructs for immunization as taught by Wittig et al., the motivation also provided by Wittig et al. that various oligopeptides can be linked to minimal expression constructs to facilitate transport of the construct into a cell, and the teachings of Wittig et al. that the YGRKKRRQRRR sequence from HIV TAT effectively mediates transduction of molecules into cells, it would have been *prima*

facie obvious to the skilled artisan at the time of filing to use a dumbbell DNA construct encoding hepatitis antigen linked to the oligopeptide YGRKKRRQRRR of Liu et al. according to the teachings of Wittig instead of a plasmid construct in the methods of immunizing against hepatitis taught by McCluskie et al. Further, based on the substantial guidance for making dumbbell constructs provided by Wittig et al., and the teachings of Wittig et al. that such constructs can be used as vaccines for infectious diseases, the skilled artisan would have had a reasonable expectation of success in making a dumbbell DNA expression construct encoding a hepatitis antigen covalently linked to a peptide such as YGRKKRRQRRR, and in administering the construct by intradermal injection as taught by McCluskie et al. to elicit immune responses in a living being.

Claim Rejections - 35 USC § 112

The rejection of claims 42-43 under 35 U.S.C. 112, second paragraph, for indefiniteness is withdrawn in view of the amendments to these claims.

Claims 42-44 are not allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, the new technology center fax number is (571) 273-8300. Please note

that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633